UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/484,594	06/07/95	O'BRIEN	J OBRIEN.002DV

EXAMINER	
HAYES,R	
ART UNIT	**PAPER NUMBER**
1812	9

DATE MAILED: 07/22/96

18N2/0722

ANITA M KIRKPATRICK
KNOBBE MARTENS OLSON & BEAR
620 NEWPORT CENTER DRIVE
SIXTEENTH FLOOR
NEWPORT BEACH CA 92660

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 6/7/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), - days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☒ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 12-25 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-11, 26-33 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 12-25 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and as failing to adequately teach how to make and/or use the invention, i.e., failing to provide an enabling disclosure.

The specification proposes a method of "treating" demyelination disorders and neuronal degenerative diseases in a mammal with an "effective" amount of prosaposin and "fragments thereof". The specification discloses three *in vitro* tissue culture studies using NS20Y neuroblastoma cells and one *ex vivo* study culturing newborn mouse cerebellar explants with saposin C and with 18-mer and 22-mer fragments of saposin C in which outgrowth of myelinated neurons increased 2-fold over control cultures. However, no disclosure is provided in the specification on "retarding nor halting" demyelination nor

neuronal degeneration; nor on *how* to assess *in vivo* "administration of an effective amount of" prosaposin, saposin C, or its 18-mer or 22-mer fragments; nor on *how* prosaposin or "fragments thereof" can "effectively" treat any of the various disease pathologies claimed.

The state of the art is such that numerous problems exist concerning effective "treatment" of neuronal disorders, because the mechanism resulting in neural degeneration and demyelination by one causative factor is not predictive of the mechanism/ treatment of degeneration/demyelination for a different causative factor. Problems also encountered before assessing whether treatment with an effective amount of prosaposin can occur within the CNS are that neuronal cell damage often results in cell death, and "administration" of nerve trophic factors to treat neurons requires solutions to not only bypassing the blood-brain barrier, but to selectively target *responsive* cells with enough trophic factor to maintain/preserve appropriate neural pathways (i.e., through specific receptor binding). Overall, the efficacy of any drug depends first on its ability to reach the desired cell population and then on finding a way to specifically bind, in this case, to the target cells. The specification discloses on page 10 that the 18-mer saposin C fragment (SEQ ID NO 5) is the *only* neurotrophic factor so far described that can cross the blood brain barrier in which uptake is approximately 0.03% (as it

relates to the scope of claims 15-17 & 23-24). This statement taken together with the disclosure that prosaposin is very water soluble (see page 22) would make it predictable that *no other* fragments would be expected to cross the blood brain barrier. Molecules that are water soluble would be predicted by the skilled artisan to *not* cross the hydrophobic blood brain barrier.

Additional problems not addressed in the specification but important obstacles to "treating mammals with an effective amount of" prosaposin are that separation of an axon from its cell body invariably results first in the degeneration of the separated portion (Wallerian degeneration; see Lieberman). In this case, "retarding or halting neuronal degeneration" also requires functional regeneration of axons already damaged (as it relates to "identifying a mammal afflicted with said disorder" in claim 12). The minimal requirement for functional regeneration is that *de novo* axonal cell growth be completed for a sufficient distance to re-establish a proximity relationship to the prior target (i.e., muscle or other synapse), which include distances of up to 1 meter for the sciatic nerve and some of the corticospinal tracts. Importantly, effective treatment requires functional regeneration (i.e., synaptogenesis) and then remyelination. Regeneration does not occur either because processes fail to grow the necessary distance, they are in competition with other nearby neuronal processes not derived from

the affected nerve, astrocytic scarring blocks axonal elongation, or because of misdirected axonal growth. Since the specification has not disclosed how to accomplish functional regeneration or *how* to "retard or halt neuronal degeneration", it can not be predicted how to use the instant invention *in vivo* without undue experimentation. This is because the *in vitro* examples and guidance provided in the specification are insufficient for the skilled artisan to successfully determine whether the above problems inherent to "effective" treatment of nervous system disorders can be overcome through administration of any neurotrophic factor, including prosaposin. In another words, the disclosed *in vitro and* single *ex vivo* study do not provide a nexus for the efficacy of prosaposin or fragments thereof to treat mammals for all claimed disorders (as it relates in particular to claims 14 and 25).

The specification does list various "disorders" of the nervous system, however, the description of how the instant invention can be used to treat these disorders with an effective amount of prosaposin is lacking with a paucity of prophetic examples on administration. For example, claim 14 recites demyelination disorders caused by "multiple sclerosis", yet the specification fails to describe the association of prosaposin treatment with the autoimmune etiology that characterizes this disease state, thereby preventing one from successfully

predicting if "treatment" would be "effective". Claim 25 recites treatment of Alzheimer's disease, but the primary neuropathology used in diagnosing Alzheimer's disease depends on its relationship to the amyloid plaques that characterize this disease. Claim 25 also recites treatment of ALS. However, ALS involves cholinergic motoneuron dysfunction versus the single cerebellar *ex vivo* example provided in the specification, in which the cerebellum contains no motoneurons and only processes inputs received from the cerebral motor cortex. Overall, the specification fails to address any of the causative factors associated with any of the other claimed neuropathological conditions, including the cell death issues that characterize Parkinson's disease, stroke, post-polio syndrome, leukoencephalitis or leukodystrophy, and how prosaposin can be used to treat them, even with *prophylactic* administration.

Taking this issue one step further, "effective administration" of prosaposin to treat these disorders can not be successfully predicted, because it is not known at what point during the course of the disease that treatment is recommended, nor how the severity of symptoms are related to the efficacy of prosaposin or for *any* "neurotrophic fragment thereof", when considering its eventual degradation by the liver. For example, Sendtner (see Baringe, 1994) found that the neurotrophic factor CNTF is quickly taken up and degraded by the liver with a half

life of 3 minutes. Moreover, in this same publication it was reported (same column on pg. 773) that Regeneron's Phase III study on CNTF to treat ALS resulted in a substantial number of those receiving CNTF having not only serious side effects, but having actually fared worse on measures of muscle strength than did patients receiving placebos. Since it is unclear how one could deliver an effective dose of the neurotrophin CNTF to any degenerating neuron *in vivo*, it is also unclear *how* the putative neurotrophic factor prosaposin could be "effectively administered to mammals". The skilled artisan could not successfully predict if the instant invention works *in vivo*, because the parameters that need to be addressed for even assaying whether the instant invention is "effective" in treating these "disorders" are incomplete or not disclosed, and based solely on *in vitro* tissue culture. In summary, these examples only more fully illustrate the undue breadth of the claims and the undue experimentation that would be required to use the instant invention, because *no specific solutions* are *proposed* for "treating a mammalian subject" suffering from *any* of the disorders recited in the claims.

Another issue is that the specification does not teach which *specific* "fragments" of prosaposin constitute "*functional* neurotrophic fragments thereof" (as it relates to claim 12). The specification fails to define what amino acids in prosaposin are

critical for the protein's function and which can be deleted/truncated (i.e., fragments) *without* affecting the protein's activity. Because of the lack of guidance provided by the specification in regards to functional fragments of prosaposin, it is not predictive to the skilled artisan what claimed molecules would constitute *functional* embodiments of the applicants' invention. Because of the extensive mutational analysis that would be required, it would constitute undue experimentation to determine such. It is suggested that limiting these fragments to saposin (SEQ ID NO 2) and its 18-mer (SEQ ID NO 5) and 22-mer fragments (SEQ ID NO 1) should obviate this one particular rejection.

Overall, because of the complexity of the issues needed to be addressed in regards to neuronal survival, growth, remyelination and administration of an effective amount of prosaposin, the claims are not commensurate in scope with that disclosed in the specification, as discussed above. In fact, there is insufficient basis to extrapolate that even other *in vitro* cultures would also be responsive to prosaposin, because the specification discloses that P12M pheochromocytoma cells are non-responsive to prosaposin (see page 14). Furthermore, it can not be successfully predicted by one skilled in the art whether the claimed embodiments of the instant invention would be responsive to putative treatment with prosaposin *in vivo*, based

on the lack of guidance disclosed in the specification concerning all of the above discussed *in vivo* issues. It is suggested that limiting the claims to promoting *in vitro* neuronal outgrowth of myelinated axons from prosaposin receptor containing cells, and from *ex vitro* newborn cerebellar explants, through treatment with the *specific* molecules depicted in SEQ ID NOs 1, 2, 3 or 5 should obviate these rejections.

Claims 12-25 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

2. Claims 18 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "degradation-inhibiting fragment" is ambiguous. It is unclear what exactly the applicant contemplates to not be degraded. Does prosaposin or its fragments degrade proteins?

Conclusion

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh, can be reached on (703) 308-2957. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Stephen Walsh

STEPHEN G. WALSH
PRIMARY EXAMINER
GROUP 1800

Robert C. Hayes, Ph.D.
July 18, 1996